

**WHAT IS CLAIMED IS:**

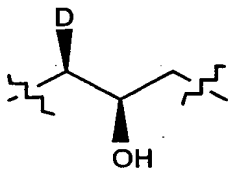
1. An HIV protease inhibitor represented by a formula:



wherein

- 5 X is a 5-7 membered non-aromatic monocyclic heterocycle, wherein said heterocycle is optionally fused or bridged with one or more 3-7 membered non-aromatic monocyclic heterocycle to form a polycyclic system, wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, or P; wherein  
10 any nitrogen forming part of the heterocycles may optionally be substituted by R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub> or O; wherein any sulfur may be optionally be substituted by one or two oxygen atoms; wherein any P may be optionally be substituted by one or more of O NR<sub>2</sub>, or S, and any of said ring systems optionally contains 1 to 6 substituents selected  
15 from the group consisting of R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, and R<sub>6</sub>;

A is ZCZNH, ZCOCONH, ZS(O)<sub>2</sub>NH, ZP(O)(V)NH, CONH, COCONH, S(O)<sub>2</sub>NH, P(O)(V)NH, wherein Z is NR<sub>2</sub>, O, S, or C(R<sub>2</sub>)<sub>2</sub>, and V is OR<sub>2</sub> or NR<sub>2</sub>;



- B is , wherein D is selected from alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or aralkyl optionally substituted with one or  
20 more groups selected from alkyl, halo, nitro, cyano, CF<sub>3</sub>, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, R<sub>6</sub>, OR<sub>2</sub>, SR<sub>2</sub>, NHR<sub>2</sub>, OR<sub>3</sub>, SR<sub>3</sub>, NHR<sub>3</sub>, OR<sub>6</sub>, SR<sub>6</sub>, or NHR<sub>6</sub>;

A' is N(D')E', wherein D' is selected from alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or aralkyl optionally substituted by alkyl, halo, nitro, cyano, CF<sub>3</sub>, O-alkyl, or S-alkyl, and E' is -CO- or -SO<sub>2</sub>-;

5 X' is selected from the group consisting of aryl and heteroaryl, which are substituted with one or more of the following groups:

OR3, OR6, OR7, OR2 provided R2 is not H or unsubstituted alkyl;

alkyl substituted by R3, R5, R6 provided R5 is not halo;

10 C2-C6 alkenyl, C2-C6 alkynyl, C3-C8 cycloalkyl, C5-C8 cycloalkenyl, and heterocyclo, which groups may be optionally substituted with one or more substituents selected from R5;

15 aryl or heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with one or more groups selected from the group consisting of aryl, heteroaryl, R2, R3, R4, and R6;

C3-C7 cycloalkyl substituted by R2, R3, R5, R6; provided R2 is not H;

CO<sub>2</sub>H or R7; provided R8 is not H or unsubstituted alkyl;

20 NR8R8, NR7R8, NR7R7; provided R8 is not H or unsubstituted alkyl;

SO<sub>n</sub>N(R8)<sub>2</sub>, SO<sub>n</sub>NR7R8, SR8, S(O)<sub>n</sub>R8, provided R8 is not H or methyl; and n is 1 or 2;

R is H or alkyl, aryl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, heteroaryl; optionally substituted by halo, hydroxy, alkoxy, aryloxy, cycloalkoxy, heteroaryloxy, cyano, nitro, alkylthio, arylthio, cycloalkylthio, amino, or mono- or dialkylamino, mono- or diarylamino, mono- or di-cycloalkylamino, mono- or di-heteroarylamino, alkanoyl, cycloalkanoyl, aroyl, heteroaroyl, carboxamido, mono- or dialkylcarboxamido, mono- or diarylcarboxamido, sulfonamido, mono- or dialkylsulfonamido, mono- or diarylsulfonamido, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, cycloalkylsulfinyl, cycloalkylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl;

R<sub>2</sub> is H or C<sub>1</sub>-C<sub>6</sub> alkyl; optionally substituted by C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>5</sub>-C<sub>8</sub> cycloalkenyl, heterocyclo; which groups may be optionally substituted with one or more substituents selected from the group consisting of halo, OR, ROH, R-halo, NO<sub>2</sub>, CN, CO<sub>n</sub>R, CON(R)<sub>2</sub>, C(S)R, C(S)N(R)<sub>2</sub>, SO<sub>n</sub>N(R)<sub>2</sub>, SR, SO<sub>n</sub>R, N(R)<sub>2</sub>, N(R)CO<sub>n</sub>R, NRS(O)<sub>n</sub>R, NRC[=N(R)]N(R)<sub>2</sub>, N(R)N(R)CO<sub>n</sub>R, NRPO<sub>n</sub>N(R)<sub>2</sub>, NRPO<sub>n</sub>OR, oxo, =N-OR, =N-N(R)<sub>2</sub>, =NR, =NNRC(O)N(R)<sub>2</sub>, =NNRCON(R)<sub>2</sub>, =NNRS(O)<sub>n</sub>N(R)<sub>2</sub>, or =NNRS(O)<sub>n</sub>(R);

or R<sub>2</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl; substituted by aryl or heteroaryl; which groups may be optionally substituted with one or more substituents selected from the group consisting of halo, OR, ROH, R-halo, NO<sub>2</sub>, CN, CO<sub>n</sub>R, CON(R)<sub>2</sub>, C(S)R, C(S)N(R)<sub>2</sub>, SO<sub>n</sub>N(R)<sub>2</sub>, SR, SO<sub>n</sub>R, N(R)<sub>2</sub>, N(R)CO<sub>n</sub>R, NRS(O)<sub>n</sub>R, NRC[=N(R)]N(R)<sub>2</sub>, N(R)N(R)CO<sub>n</sub>R, NRPO<sub>n</sub>N(R)<sub>2</sub>, NRPO<sub>n</sub>OR;

or R2 is C1-C6 alkyl; optionally substituted by halo, OR, ROH, R-halo, NO<sub>2</sub>, CN, CO<sub>n</sub>R, CON(R)<sub>2</sub>, C(S)R, C(S)N(R)<sub>2</sub>, SO<sub>n</sub>N(R)<sub>2</sub>, SR, SO<sub>n</sub>R, N(R)<sub>2</sub>, N(R)CO<sub>n</sub>R, NRS(O)<sub>n</sub>R, NRC[=N(R)]N(R)<sub>2</sub>, N(R)N(R)CO<sub>n</sub>R, NRPO<sub>n</sub>N(R)<sub>2</sub>, NRPO<sub>n</sub>OR, oxo, =N-OR, =N-N(R)<sub>2</sub>, =NR, =NNRC(O)N(R)<sub>2</sub>, =NNRCONR, =NNRS(O)<sub>n</sub>N(R)<sub>2</sub>, or =NNRS(O)<sub>n</sub>(R);

R3 is C2-C6 alkenyl, C2-C6 alkynyl, C3-C8 cycloalkyl, C5-C8 cycloalkenyl, or heterocyclo; which groups may be optionally substituted with one or more substituents selected from the group consisting of halo, OR<sub>2</sub>, R<sub>2</sub>-OH, R<sub>2</sub>-halo, NO<sub>2</sub>, CN, CO<sub>n</sub>R<sub>2</sub>, C(O)N(R<sub>2</sub>)<sub>2</sub>, C(O)N(R<sub>2</sub>)N(R<sub>2</sub>)<sub>2</sub>, C(S)R<sub>2</sub>, C(S)N(R<sub>2</sub>)<sub>2</sub>, S(O)<sub>n</sub>N(R<sub>2</sub>)<sub>2</sub>, SR<sub>2</sub>, SO<sub>n</sub>R<sub>2</sub>, N(R)<sub>2</sub>, N(R<sub>2</sub>)CO<sub>n</sub>R<sub>2</sub>, NR<sub>2</sub>S(O)<sub>n</sub>R<sub>2</sub>, NR<sub>2</sub>C[=N(R<sub>2</sub>)]N(R<sub>2</sub>)<sub>2</sub>, N(R<sub>2</sub>)N(R<sub>2</sub>)CO<sub>n</sub>R<sub>2</sub>, NR<sub>2</sub>PO<sub>n</sub>N(R<sub>2</sub>)<sub>2</sub>, NR<sub>2</sub>PO<sub>n</sub>OR<sub>2</sub>, oxo, =N-OR<sub>2</sub>, =N-N(R<sub>2</sub>)<sub>2</sub>, =NR<sub>2</sub>, =NNRC(O)N(R<sub>2</sub>)<sub>2</sub>, =NNR<sub>2</sub>C(O)<sub>n</sub>R<sub>2</sub>, =NNR<sub>2</sub>S(O)<sub>n</sub>N(R<sub>2</sub>)<sub>2</sub>, or =NNR<sub>2</sub>S(O)<sub>n</sub>(R<sub>2</sub>);

R4 is halo, OR<sub>8</sub>, R<sub>2</sub>-OH, R<sub>3</sub>-OH, R<sub>2</sub>-halo, R<sub>3</sub>-halo, NO<sub>2</sub>, CN, CO<sub>n</sub>R<sub>8</sub>, CO<sub>n</sub>R<sub>8</sub>, CON(R<sub>8</sub>)<sub>2</sub>, C(O)N(R<sub>8</sub>)N(R<sub>8</sub>)<sub>2</sub>, C(S)R<sub>8</sub>, C(S)N(R<sub>8</sub>)<sub>2</sub>, SO<sub>n</sub>N(R<sub>8</sub>)<sub>2</sub>, SR<sub>8</sub>, SO<sub>n</sub>R<sub>8</sub>, N(R<sub>8</sub>)<sub>2</sub>, N(R<sub>8</sub>)CO<sub>n</sub>R<sub>8</sub>, NR<sub>8</sub>S(O)<sub>n</sub>R<sub>8</sub>, NR<sub>8</sub>C[=N(R<sub>8</sub>)]N(R<sub>8</sub>)<sub>2</sub>, N(R<sub>8</sub>)N(R<sub>8</sub>)CO<sub>n</sub>R<sub>8</sub>, NR<sub>8</sub>PO<sub>n</sub>N(R<sub>8</sub>)<sub>2</sub>, NR<sub>8</sub>PO<sub>n</sub>OR<sub>8</sub>, OC(O)R<sub>2</sub>, OC(S)R<sub>8</sub>, OC(O)N(R<sub>8</sub>)<sub>2</sub>, OC(S)N(R<sub>8</sub>)<sub>2</sub>, OPO<sub>n</sub>(R<sub>8</sub>)<sub>2</sub>;

R5 is OR<sub>8</sub>, N(R<sub>8</sub>)<sub>2</sub>, NHOH, N(R<sub>8</sub>)COR<sub>8</sub>, NR<sub>8</sub>S(O)<sub>n</sub>R<sub>8</sub>, NR<sub>8</sub>C[=N(R<sub>8</sub>)]N(R<sub>8</sub>)<sub>2</sub>, N(R<sub>8</sub>)N(R<sub>8</sub>)C(O)R<sub>8</sub>, NR<sub>8</sub>PO<sub>n</sub>N(R<sub>8</sub>)<sub>2</sub>, NR<sub>8</sub>PO<sub>n</sub>OR<sub>8</sub>, R<sub>2</sub>OH, R<sub>3</sub>-OH, R<sub>2</sub>-halo, R<sub>3</sub>-halo, CN, CO<sub>n</sub>R<sub>8</sub>; provided that when n = 2, R<sub>8</sub> is not H; CON(R<sub>8</sub>)<sub>2</sub>, C(O)N(R<sub>8</sub>)N(R<sub>8</sub>)<sub>2</sub>, C(S)<sub>n</sub>R<sub>8</sub>, C(S)N(R<sub>8</sub>)<sub>2</sub>, S(O)<sub>n</sub>R<sub>8</sub>, SO<sub>n</sub>N(R<sub>8</sub>)<sub>2</sub>, halo, NO<sub>2</sub>, SR<sub>8</sub>, oxo, =N-

OH, =N-OR<sub>8</sub>, =N-N(R<sub>8</sub>)<sub>2</sub>, =NR<sub>8</sub>, =NNR<sub>8</sub>C(O)N(R<sub>8</sub>)<sub>2</sub>,  
 =NNR<sub>8</sub>C(O)<sub>n</sub>R<sub>8</sub>, =NNR<sub>8</sub>S(O)<sub>n</sub>N(R<sub>8</sub>)<sub>2</sub>, or =NNR<sub>8</sub>S(O)<sub>n</sub>(R<sub>8</sub>), or R<sub>3</sub>

R<sub>6</sub> is aryl or heteroaryl, wherein said aryl or heteroaryl may be  
 optionally substituted with one or more groups selected from aryl,  
 heteroaryl, R<sub>2</sub>, R<sub>3</sub>, halo, OR<sub>2</sub>, R<sub>2</sub>OH, R<sub>2</sub>-halo, NO<sub>2</sub>, CN, CO<sub>n</sub>R<sub>2</sub>,  
 C(O)N(R<sub>2</sub>)<sub>2</sub>, C(O)N(R<sub>2</sub>)N(R<sub>2</sub>)<sub>2</sub>, C(S)R<sub>2</sub>, C(S)N(R<sub>2</sub>)<sub>2</sub>, S(O)<sub>n</sub>N(R<sub>2</sub>)<sub>2</sub>,  
 SR<sub>2</sub>, SO<sub>n</sub>R<sub>2</sub>, N(R<sub>2</sub>)<sub>2</sub>, N(R<sub>2</sub>)CO<sub>n</sub>R<sub>2</sub>, NR<sub>2</sub>S(O)<sub>n</sub>R<sub>2</sub>,  
 NR<sub>2</sub>C[=N(R<sub>2</sub>)]N(R<sub>2</sub>)<sub>2</sub>, N(R<sub>2</sub>)N(R<sub>2</sub>)CO<sub>n</sub>R<sub>2</sub>, NR<sub>2</sub>PO<sub>n</sub>N(R<sub>2</sub>)<sub>2</sub>,  
 NR<sub>2</sub>PO<sub>n</sub>OR<sub>2</sub>, OC(O)R<sub>2</sub>, OC(S)R<sub>2</sub>, OC(O)N(R<sub>2</sub>)<sub>2</sub>, OC(S)N(R<sub>2</sub>)<sub>2</sub>,  
 OPO<sub>n</sub>(R<sub>2</sub>)<sub>2</sub>

R<sub>7</sub> is C(O)<sub>n</sub>R<sub>8</sub>; provided that when n = 2; R<sub>8</sub> is not H; C(S)R<sub>8</sub>,  
 C(O)N(R<sub>8</sub>)<sub>2</sub>, C(S)N(R<sub>8</sub>)<sub>2</sub>, S(O)<sub>n</sub>R<sub>8</sub>, S(O)<sub>n</sub>N(R<sub>8</sub>)<sub>2</sub>;

R<sub>8</sub> is R<sub>2</sub>, R<sub>3</sub>, or R<sub>6</sub>;

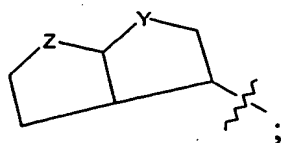
each n is independently 1 or 2;

its stereoisomeric forms; and

its pharmacologically acceptable salts.

2. The compound according to claim 1, wherein

X is



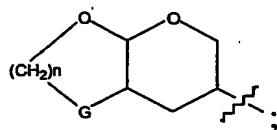
Y is O, NH, or S;

Z is O, NH, or S; and

wherein any ring carbon is optionally substituted by R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, or R<sub>6</sub>.

5 3. The compound according to claim 1, wherein

X is



wherein

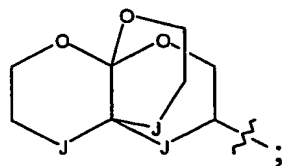
G is C, O, NR<sub>2</sub>, or S;

10 n is an integer between 1-2; and

wherein any ring carbon is optionally substituted by R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, or R<sub>6</sub>.

4. The compound according to claim 1, wherein

X is



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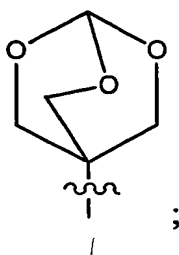
wherein

J is independently CH<sub>2</sub>, or O, and

wherein any ring carbon is optionally substituted by R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, or R<sub>6</sub>.

5. The compound according to claim 1, wherein:

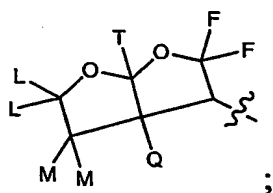
X is



wherein any ring carbon is optionally substituted by R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, or R<sub>6</sub>.

6. The compound according to claim 1, wherein

X is



wherein

each L is independently H, lower alkyl, oxo, or L forms a carbocyclic or heterocyclic ring with M;

each M is independently H, OH, chloro, fluoro, or M forms a carbocyclic or heterocyclic ring with Q, provided that if one M is OH, the other M is not OH;

Q is H, OH, amino, lower alkyl, alkylamino, alkoxy, halo, or forms a 3-7-membered carbocyclic or heterocyclic ring together with T;

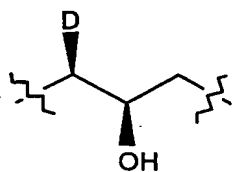
5 each F is independently H, OH, lower alkyl, halo, or spirocyclopropyl, provided that if one R is OH, the other R is not OH;

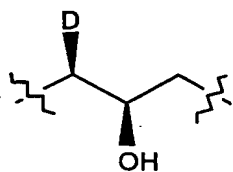
T is H or F, or T forms a carbocyclic or heterocyclic ring together with F.

7. The HIV protease inhibitor according to claim 1, wherein

10 X is tetrahydrofurodihydrofuranyl, tetrahydrofurotetrahydrofuranyl, tetrahydropyranotetrahydrofuranyl or tetrahydropyranodihydrofuranyl;

A is OCONH;



15 B is , wherein D is selected from alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or aralkyl optionally substituted with one or more groups selected from alkyl, halo, nitro, cyano, CF<sub>3</sub>, C3-C7 cycloalkyl, C5-C7 cycloalkenyl, R<sub>6</sub>, OR<sub>2</sub>, SR<sub>2</sub>, NHR<sub>2</sub>, OR<sub>3</sub>, SR<sub>3</sub>, NHR<sub>3</sub>, OR<sub>6</sub>, SR<sub>6</sub>, or NHR<sub>6</sub>; and

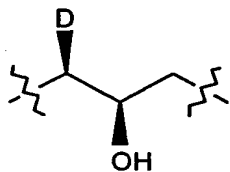
20 A' is N(D')E', wherein D' is alkyl, alkenyl, alkynyl aryl, cycloalkyl, or aralkyl optionally substituted by alkyl, halo, or CF<sub>3</sub>, and E' is -SO<sub>2</sub>-.

8. The HIV protease inhibitor according to claim 1, wherein:



X is tetrahydrofurotetrahydrofuranyl;

A is OCONH;



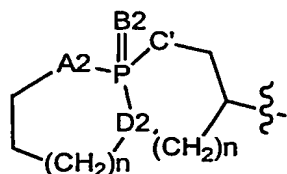
B is , wherein D is benzyl; and

A' is N(D')E', wherein D' is isobutyl and E' is -SO<sub>2</sub>-;

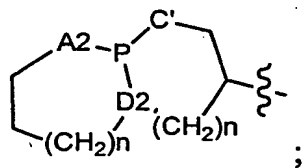
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9. The HIV protease inhibitor according to claim 1, wherein

X is



or



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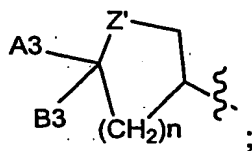
wherein A2, B2, and C' are each independently O, NR<sub>2</sub>, or S;

D2 is CH or N; and

n is an integer between 1 and 2.

10. The HIV protease inhibitor according to claim 1, wherein:

X is



wherein

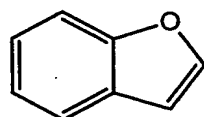
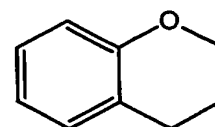
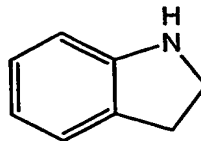
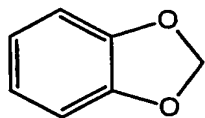
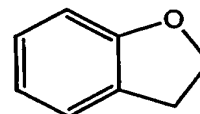
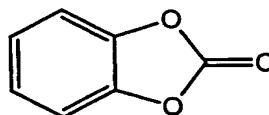
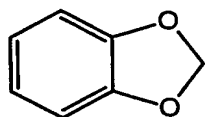
5 A3 is H, F or alkoxy;

B3 is F, alkoxy, lower alkyl, or A3 and B3 can form a 3-7 membered heterocyclic ring;

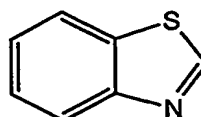
Z' is O, NR<sub>2</sub>, or S; and

n is an integer between 1-3.

10 11. The HIV protease inhibitor of claim 1, wherein X' is selected from



or



;

wherein said groups are substituted with one or more of the following groups:

OR3, OR6, OR7, OR2 provided R2 is not H or unsubstituted alkyl;

alkyl substituted by R3, R5, R6 provided R5 is not halo;

C2-C6 alkenyl, C2-C6 alkynyl, C3-C8 cycloalkyl, C5-C8 cycloalkenyl, and heterocyclo, which groups may be optionally substituted with one or more substituents selected from R5;

aryl or heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with one or more groups selected from the group consisting of aryl, heteroaryl, R2, R3, R4, and R6;

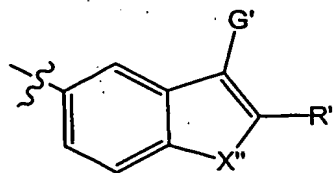
C3-C7 cycloalkyl substituted by R2, R3, R5, R6; provided R2 is not H;

CO<sub>2</sub>H or R7; provided R8 is not H or unsubstituted alkyl;

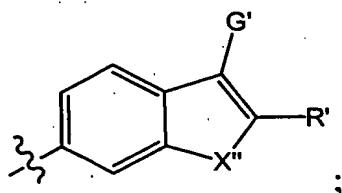
NR<sub>8</sub>R<sub>8</sub>, NR<sub>7</sub>R<sub>8</sub>, NR<sub>7</sub>R<sub>7</sub>; provided R8 is not H or unsubstituted alkyl; and

SO<sub>n</sub>N(R<sub>8</sub>)<sub>2</sub>, SO<sub>n</sub>NR<sub>7</sub>R<sub>8</sub>, SR<sub>8</sub>, S(O)<sub>n</sub>R<sub>8</sub>, provided R<sub>8</sub> is not H or methyl; and n is 1 or 2.

12. The HIV protease inhibitor of claim 1, wherein X' is selected from



or



wherein

5         $G'$  and  $R'$  cannot both be H;

$G'$  and  $R'$  are each independently:

H or alkyl substituted by  $R_3$ ,  $R_5$ ,  $R_6$  provided  $R_5$  is not halo;

10        C2-C6 alkenyl, C2-C6 alkynyl, C3-C8 cycloalkyl, C5-C8 cycloalkenyl, and heterocyclo, which groups may be optionally substituted with one or more substituents selected from the group consisting of  $-OR_2$ ,  $C(O)N(R_2)_2$ ,  $S(O)_nN(R_2)_2$ , CN,  $SR_2$ ,  $SO_nR_2$ ,  $COR_2$ ,  $CO_2R_2$  or  $NR_2C(O)R_2$ ,  $R_5$ , and  $R_7$ ;

15        aryl or heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with one or more groups selected from the group consisting of aryl, heteroaryl,  $R_2$ ,  $R_3$ ,  $R_4$ , and  $R_6$ ;

C3-C7 cycloalkyl substituted by  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ ; provided  $R_2$  is not H;

$CO_2H$  or  $R_7$  provided  $R_2$  is not H or unsubstituted alkyl;

$\text{SO}_n\text{N}(\text{R}_8)_2$ ,  $\text{SO}_n\text{NR}_7\text{R}_8$ ,  $\text{SR}_8$ ,  $\text{S}(\text{O})_n\text{R}_8$ , provided  $\text{R}_8$  is not H or methyl; and  $n$  is 1 or 2;

and  $\text{X}''$  is selected from O or  $\text{NR}''$ ;

wherein  $\text{R}''$  is

5

H or alkyl optionally substituted by  $\text{R}_3$ ,  $\text{R}_5$ ,  $\text{R}_6$ ;

10

C2-C6 alkenyl, C2-C6 alkynyl, C3-C8 cycloalkyl, C5-C8 cycloalkenyl, and heterocyclo, which groups may be optionally substituted with one or more substituents selected from the group consisting of  $-\text{OR}_2$ ,  $\text{C}(\text{O})\text{N}(\text{R}_2)_2$ ,  $\text{S}(\text{O})_n\text{N}(\text{R}_2)_2$ , CN,  $\text{SR}_2$ ,  $\text{SO}_n\text{R}_2$ ,  $\text{COR}_2$ ,  $\text{CO}_2\text{R}_2$  or  $\text{NR}_2\text{C}(\text{O})\text{R}_2$ ,  $\text{R}_5$ , and  $\text{R}_7$ ;

15

aryl or heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with one or more groups selected from the group consisting of aryl, heteroaryl,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$ , and  $\text{R}_6$ ;

20

C3-C7 cycloalkyl optionally substituted by  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_5$ ,  $\text{R}_6$ ;

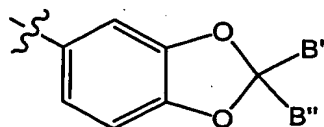
$\text{R}_7$ ;

$\text{NR}_3\text{R}_3$ ,  $\text{NR}_6\text{R}_6$ ,  $\text{NR}_7\text{R}_7$ ,  $\text{NR}_3\text{R}_6$ ,  $\text{NR}_6\text{R}_7$ ,  $\text{NR}_3\text{R}_7$ ,  $\text{NR}_2\text{R}_3$ ,  $\text{NR}_2\text{R}_6$ ,  $\text{NR}_2\text{R}_7$ ,  $\text{NR}_2\text{R}_2$ ;

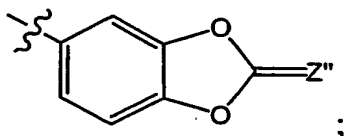
$\text{SO}_n\text{N}(\text{R}_2)_2$ ,  $\text{SO}_n\text{N}(\text{R}_3)_2$ ,  $\text{SO}_n\text{N}(\text{R}_6)_2$ ,  $\text{SO}_n\text{N}(\text{R}_7)_2$ ,  $\text{SO}_n\text{NR}_2\text{R}_3$ ,  $\text{SO}_n\text{NR}_2\text{R}_6$ ,  $\text{SO}_n\text{NR}_2\text{R}_7$ ,  $\text{SO}_n\text{NR}_3\text{R}_6$ ,  $\text{SO}_n\text{NR}_3\text{R}_7$ ,  $\text{SO}_n\text{NR}_6\text{R}_7$ ;

$S(O)_mR_2$ ,  $S(O)_mR_3$ ,  $S(O)_mR_6$ , provided  $R_2$  is not H; and  $m$  is 0, 1 or 2.

13. The HIV protease inhibitor of claim 1, wherein  $X'$  is selected from



or



wherein

$B'$  and  $B''$  cannot both be H or methyl;

10  $B'$  and  $B''$  are independently:

H or alkyl optionally substituted by  $R_3$ ,  $R_5$ ,  $R_6$ ;

15 C2-C6 alkenyl, C2-C6 alkynyl, C3-C8 cycloalkyl, C5-C8 cycloalkenyl, and heterocyclo, which groups may be optionally substituted with one or more substituents selected from the group consisting of  $-OR_2$ ,  $C(O)N(R_2)_2$ ,  $S(O)_nN(R_2)_2$ , CN,  $SR_2$ ,  $SO_nR_2$ ,  $COR_2$ ,  $CO_2R_2$  or  $NR_2C(O)R_2$ ,  $R_5$ , and  $R_7$ ;

aryl or heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with one or more groups selected from the group consisting of aryl, heteroaryl,  $R_2$ ,  $R_3$ ,  $R_4$ , and  $R_6$ ;

C3-C7 cycloalkyl optionally substituted by R2, R3, R5, R6;

CO<sub>2</sub>H or R7;

SO<sub>n</sub>N(R2)<sub>2</sub>, SO<sub>n</sub>N(R3)<sub>2</sub>, SO<sub>n</sub>N(R6)<sub>2</sub>, SO<sub>n</sub>N(R7)<sub>2</sub>, SO<sub>n</sub>NR2R3,  
SO<sub>n</sub>NR2R6, SO<sub>n</sub>NR2R7, SO<sub>n</sub>NR3R6, SO<sub>n</sub>NR3R7, SO<sub>n</sub>NR6R7;

5 S(O)<sub>m</sub>R2, S(O)<sub>m</sub>R3, S(O)<sub>m</sub>R6; and m is 0, 1 or 2;

Z" is O, NR9;

R9 is

alkyl optionally substituted by R3, R5, R6;

10 C2-C6 alkenyl, C2-C6 alkynyl, C3-C8 cycloalkyl, C5-C8  
cycloalkenyl, and heterocyclo, which groups may be optionally  
substituted with one or more substituents selected from the  
group consisting of -OR2, C(O)N(R2)<sub>2</sub>, S(O)<sub>n</sub>N(R2)<sub>2</sub>, CN, SR2,  
SO<sub>n</sub>R2, COR2, CO<sub>2</sub>R2 or NR2C(O)R2, R5, and R7;

15 aryl or heteroaryl, wherein said aryl or heteroaryl may be  
optionally substituted with one or more groups selected from the  
group consisting of aryl, heteroaryl, R2, R3, R4, and R6;

C3-C7 cycloalkyl optionally substituted by R2, R3, R5, R6;

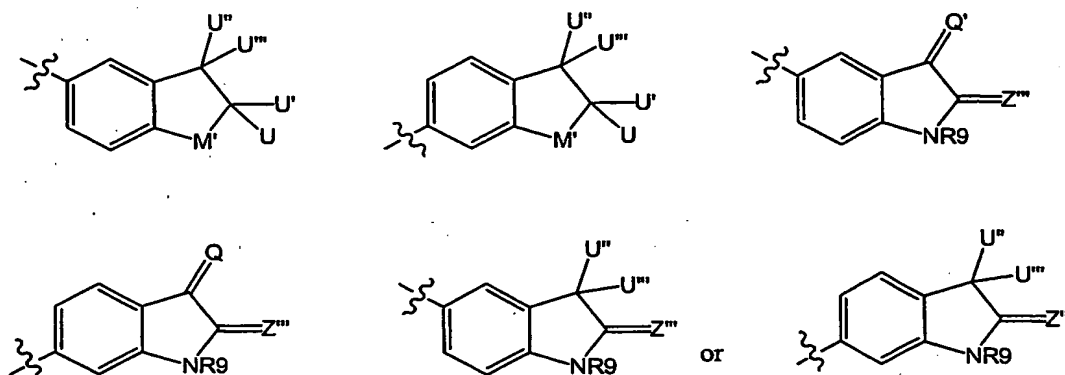
CO<sub>2</sub>H or R7;

20 NR3R3, NR6R6, NR7R7, NR3R6, NR6R7, NR3R7, NR2R3,  
NR2R6, NR2R7, NR2R2;

SO<sub>n</sub>N(R2)<sub>2</sub>, SO<sub>n</sub>N(R3)<sub>2</sub>, SO<sub>n</sub>N(R6)<sub>2</sub>, SO<sub>n</sub>N(R7)<sub>2</sub>, SO<sub>n</sub>NR2R3,  
SO<sub>n</sub>NR2R6, SO<sub>n</sub>NR2R7, SO<sub>n</sub>NR3R6, SO<sub>n</sub>NR3R7, SO<sub>n</sub>NR6R7;

$S(O)_mR_2$ ,  $S(O)_mR_3$ ,  $S(O)_mR_6$ , provided  $R_2$  is not H; and  $m$  is 0, 1 or 2.

14. The HIV protease inhibitor of claim 1, wherein  $X'$  is selected from



$U$  and  $U'$  are each independently

H or alkyl substituted by  $R_3$ ,  $R_5$ ,  $R_6$ ;

10 C2-C6 alkenyl, C2-C6 alkynyl, C3-C8 cycloalkyl, C5-C8 cycloalkenyl, and heterocyclo, which groups may be optionally substituted with one or more substituents selected from the group consisting of  $-OR_2$ ,  $C(O)N(R_2)_2$ ,  $S(O)_nN(R_2)_2$ , CN,  $SR_2$ ,  $SO_nR_2$ ,  $COR_2$ ,  $CO_2R_2$  or  $NR_2C(O)R_2$ ,  $R_5$ , and  $R_7$ ;

15 aryl or heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with one or more groups selected from the group consisting of aryl, heteroaryl,  $R_2$ ,  $R_3$ ,  $R_4$ , and  $R_6$ ;

C3-C7 cycloalkyl substituted by  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ ;



CO<sub>2</sub>H, R7;

SO<sub>n</sub>N(R<sub>2</sub>)<sub>2</sub>, SO<sub>n</sub>N(R<sub>3</sub>)<sub>2</sub>, SO<sub>n</sub>N(R<sub>6</sub>)<sub>2</sub>, SO<sub>n</sub>N(R<sub>7</sub>)<sub>2</sub>, SO<sub>n</sub>NR<sub>2</sub>R<sub>3</sub>,  
SO<sub>n</sub>NR<sub>2</sub>R<sub>6</sub>, SO<sub>n</sub>NR<sub>2</sub>R<sub>7</sub>, SO<sub>n</sub>NR<sub>3</sub>R<sub>6</sub>, SO<sub>n</sub>NR<sub>3</sub>R<sub>7</sub>, SO<sub>n</sub>NR<sub>6</sub>R<sub>7</sub>,  
wherein n= 1 or 2;

5 S(O)<sub>m</sub>R<sub>2</sub>, S(O)<sub>m</sub>R<sub>3</sub>, S(O)<sub>m</sub>R<sub>6</sub>, provided R<sub>2</sub> is not H; and n is 0,  
1 or 2;

U'' and U''' are each independently

H, OR<sub>3</sub>, OR<sub>6</sub>, OR<sub>7</sub>, OR<sub>2</sub>;

alkyl substituted by R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>;

10 C2-C6 alkenyl, C2-C6 alkynyl, C3-C8 cycloalkyl, C5-C8  
cycloalkenyl, and heterocyclo, which groups may be optionally  
substituted with one or more substituents selected from the  
group consisting of -OR<sub>2</sub>, C(O)N(R<sub>2</sub>)<sub>2</sub>, S(O)<sub>n</sub>N(R<sub>2</sub>)<sub>2</sub>, CN, SR<sub>2</sub>,  
SO<sub>n</sub>R<sub>2</sub>, COR<sub>2</sub>, CO<sub>2</sub>R<sub>2</sub> or NR<sub>2</sub>C(O)R<sub>2</sub>, R<sub>5</sub>, and R<sub>7</sub>;

15 aryl or heteroaryl, wherein said aryl or heteroaryl may be  
optionally substituted with one or more groups selected from the  
group consisting of aryl, heteroaryl, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>6</sub>;

C3-C7 cycloalkyl substituted by R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>;

CO<sub>2</sub>H or R<sub>7</sub>;

20 NR<sub>3</sub>R<sub>3</sub>, NR<sub>6</sub>R<sub>6</sub>, NR<sub>7</sub>R<sub>7</sub>, NR<sub>3</sub>R<sub>6</sub>, NR<sub>6</sub>R<sub>7</sub>, NR<sub>3</sub>R<sub>7</sub>, NR<sub>2</sub>R<sub>3</sub>,  
NR<sub>2</sub>R<sub>6</sub>, NR<sub>2</sub>R<sub>7</sub>, NR<sub>2</sub>R<sub>2</sub>;

SO<sub>n</sub>N(R<sub>2</sub>)<sub>2</sub>, SO<sub>n</sub>N(R<sub>3</sub>)<sub>2</sub>, SO<sub>n</sub>N(R<sub>6</sub>)<sub>2</sub>, SO<sub>n</sub>N(R<sub>7</sub>)<sub>2</sub>, SO<sub>n</sub>NR<sub>2</sub>R<sub>3</sub>,  
SO<sub>n</sub>NR<sub>2</sub>R<sub>6</sub>, SO<sub>n</sub>NR<sub>2</sub>R<sub>7</sub>, SO<sub>n</sub>NR<sub>3</sub>R<sub>6</sub>, SO<sub>n</sub>NR<sub>3</sub>R<sub>7</sub>, SO<sub>n</sub>NR<sub>6</sub>R<sub>7</sub>;

$S(O)_mR_2$ ,  $S(O)_mR_3$ ,  $S(O)_mR_6$ , provided  $R_2$  is not H; and  $m$  is 0, 1 or 2;

$U$  and  $U'$  cannot both be H unless one of  $U''$  and  $U'''$  is not H;

$U''$  and  $U'''$  cannot both be H unless one of  $U$  and  $U'$  is not H;

5  $M'$  is O,  $NR_9$ , or NH, except where  $R_9$  is  $CO_2H$

$Z'''$  is O or  $NR_9$

$Q'$  is O,  $NR_9$ , or  $CU''U'''$ ;

$R_9$  is

alkyl optionally substituted by  $R_3$ ,  $R_5$ ,  $R_6$ ;

10  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_3$ - $C_8$  cycloalkyl,  $C_5$ - $C_8$  cycloalkenyl, and heterocyclo, which groups may be optionally substituted with one or more substituents selected from the group consisting of  $-OR_2$ ,  $C(O)N(R_2)_2$ ,  $S(O)_nN(R_2)_2$ , CN,  $SR_2$ ,  $SO_nR_2$ ,  $COR_2$ ,  $CO_2R_2$  or  $NR_2C(O)R_2$ ,  $R_5$ , and  $R_7$ ;

15 aryl or heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with one or more groups selected from the group consisting of aryl, heteroaryl,  $R_2$ ,  $R_3$ ,  $R_4$ , and  $R_6$ ;

$C_3$ - $C_7$  cycloalkyl optionally substituted by  $R_2$ ,  $R_3$ ,  $R_5$ ,  $R_6$ ;

$CO_2H$  or  $R_7$ ;

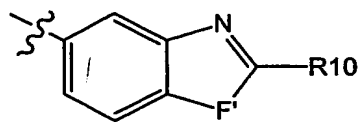
20  $NR_3R_3$ ,  $NR_6R_6$ ,  $NR_7R_7$ ,  $NR_3R_6$ ,  $NR_6R_7$ ,  $NR_3R_7$ ,  $NR_2R_3$ ,  $NR_2R_6$ ,  $NR_2R_7$ ,  $NR_2R_2$ ;

$\text{SO}_n\text{N}(\text{R}_2)_2$ ,  $\text{SO}_n\text{N}(\text{R}_3)_2$ ,  $\text{SO}_n\text{N}(\text{R}_6)_2$ ,  $\text{SO}_n\text{N}(\text{R}_7)_2$ ,  $\text{SO}_n\text{NR}_2\text{R}_3$ ,  
 $\text{SO}_n\text{NR}_2\text{R}_6$ ,  $\text{SO}_n\text{NR}_2\text{R}_7$ ,  $\text{SO}_n\text{NR}_3\text{R}_6$ ,  $\text{SO}_n\text{NR}_3\text{R}_7$ ,  $\text{SO}_n\text{NR}_6\text{R}_7$ ;

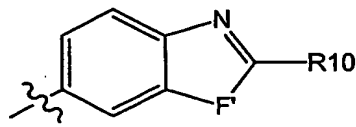
$\text{S}(\text{O})_m\text{R}_2$ ,  $\text{S}(\text{O})_m\text{R}_3$ ,  $\text{S}(\text{O})_m\text{R}_6$ , provided  $\text{R}_2$  is not H; and  $m$  is 0,  
 1 or 2.

5

15. The HIV protease inhibitor of claim 1, wherein  $\text{X}'$  is selected  
 from



or



10

wherein

$\text{R}_{10}$  is

alkyl substituted by  $\text{R}_3$ ,  $\text{R}_5$ ,  $\text{R}_6$  provided  $\text{R}_5$  is not halo;

$\text{C}_2$ - $\text{C}_6$  alkenyl,  $\text{C}_2$ - $\text{C}_6$  alkynyl,  $\text{C}_3$ - $\text{C}_8$  cycloalkyl,  $\text{C}_5$ - $\text{C}_8$   
 cycloalkenyl, and heterocyclo, which groups may be optionally  
 substituted with one or more substituents selected from the  
 group consisting of  $-\text{OR}_2$ ,  $\text{C}(\text{O})\text{N}(\text{R}_2)_2$ ,  $\text{S}(\text{O})_n\text{N}(\text{R}_2)_2$ ,  $\text{CN}$ ,  $\text{SR}_2$ ,  
 $\text{SO}_n\text{R}_2$ ,  $\text{COR}_2$ ,  $\text{CO}_2\text{R}_2$  or  $\text{NR}_2\text{C}(\text{O})\text{R}_2$ ,  $\text{R}_5$ , and  $\text{R}_7$ ;

15

aryl or heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with one or more groups selected from the group consisting of aryl, heteroaryl, R2, R3, R4, and R6;

C3-C7 cycloalkyl substituted by R2, R3, R5, R6; provided R2 is not H;

R7 provided Z is N, O, S and provided R2 is not H or unsubstituted alkyl; and

F' is O or S.

10            16.    A compound according to claim 1, bound in a complex with wild type or drug resistant mutant forms of HIV-1 protease.

17.    A pharmaceutical composition comprising an effective amount of an inhibitor according to claim 1 and a pharmaceutically acceptable additive, excipient, or diluent.

15            18.    A pharmaceutical composition comprising an effective amount inhibitor according to claim 1 and another antiretroviral agent.

19.    A pharmaceutical composition comprising an effective amount of an inhibitor according to claim 1 and a second HIV inhibitor.

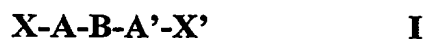
20            20.    A pharmaceutical composition comprising an inhibitor according to claim 1 and an additional HIV protease inhibitor.

21.    A pharmaceutical composition comprising an effective amount of an inhibitor according to claim 1 and an HIV reverse transcriptase inhibitor.

22. A method of treating a patient suffering from HIV infection, comprising administering to said patient a composition according to claim 1.

23. A method of treatment according to claim 22 wherein said patient is suffering from a multi-drug resistant HIV infection.

24. An HIV protease inhibitor having the formula I:



wherein X is a moiety comprising first and second hydrogen bond acceptor atoms  $\text{H}_{\text{A1}}\text{:X}$  and  $\text{H}_{\text{A2}}\text{:X}$ , wherein  $\text{H}_{\text{A1}}\text{:X}$  forms a hydrogen bond with N29 of HIV protease and  $\text{H}_{\text{A2}}\text{:X}$  forms a hydrogen bond with N30 of HIV protease at the relative positions designated in Table 8;

wherein A is an optionally substituted linker moiety comprising a linear chain of 2-6 atoms, wherein A comprises a hydrogen bond acceptor atom  $\text{H}_{\text{A}}\text{:A}$ , and a hydrogen bond donor atom  $\text{H}_{\text{D}}\text{:A}$ , and wherein  $\text{H}_{\text{A}}\text{:A}$  forms a hydrogen bond with solvated water<sup>301</sup> of said protease at a relative position designated by O301, and  $\text{H}_{\text{D}}\text{:A}$  forms a hydrogen bond with the backbone CO atom of residue 27 of said protease at a relative position designated by O27;

wherein B comprises a hydrogen bond donor or acceptor atom  $\text{H}_{\text{D/A}}\text{:B}$ , wherein  $\text{H}_{\text{D/A}}\text{:B}$  forms a hydrogen bond with either or both carboxylate side chain oxygens of Asp25 and Asp 125 of said protease at relative positions designated by OD1 25, OD2 25, OD1 125, and OD2 125;

wherein A' is an optionally substituted linker moiety comprising a linear chain of 2-6 atoms, comprising a hydrogen bond acceptor atom  $H_A:A'$ , wherein  $H_A:A'$  forms a hydrogen bond with solvated water<sup>301</sup> of said protease at a relative position designated by O301; and

5 wherein X' is a moiety comprising a hydrogen bond acceptor atom  $H_A:X'$ , wherein  $H_A:X'$  forms a hydrogen bond with backbone NH atoms of residues 129 and/or 130 of said protease at relative positions designated by N129 and/or N130.

10 25. A compound according to claim 24, bound in a complex with wild type or drug resistant mutant forms of HIV-1 protease.

26. A pharmaceutical composition comprising an effective amount of an inhibitor according to claim 24 and a pharmaceutically acceptable additive, excipient, or diluent.

15 27. A pharmaceutical composition comprising an effective amount inhibitor according to claim 24 and another antiretroviral agent.

28. A pharmaceutical composition comprising an effective amount of an inhibitor according to claim 24 and a second HIV inhibitor.

20 29. A pharmaceutical composition comprising an inhibitor according to claim 24 and an additional HIV protease inhibitor.

30. A pharmaceutical composition comprising an effective amount of an inhibitor according to claim 24 and an HIV reverse transcriptase inhibitor.

31. A method of treating a patient suffering from HIV infection, comprising administering to said patient a composition according to claim 24.

5 32. A method of treatment according to claim 31 wherein said patient is suffering from a multi-drug resistant HIV infection.